IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application f : Box AF

Robert M. LORENCE ET AL. : Group Art Unit: 1813

Serial No.: 08/260,536 : Examiner: L. Scheiner

Filed: June 16, 1994 :

For: METHODS FOR TREATING AND DETECTING CANCER USING VIRUSES

DECLARATION UNDER § 1.132 OF DR. CONRAD HEILMAN

I, CONRAD HEILMAN, declare and state as follows:

1. I am a citizen of the United States, residing at 10 Granby Road, Landenberg, PA 19350.

2. I presently hold the position of Vice President of Research at Pro-Virus, Inc., 1530 E. Jefferson Street, Rockville, Maryland, where I have been employed since October 24, 1994.

3. I obtained a Ph.D. in Virology in 1982 from The Johns Hopkins University. A copy of my curriculum vitae is attached, demonstrating my expertise to make this declaration.

4. I have read the originally-filed patent applications, U.S. Serial Nos. 08/055,519 and 08/260,536. Each of these disclosures clearly conveys to a skilled worker familiar with NDV viruses the concept of treating and detecting cancer with a mesogenic strain of Newcastle Disease Virus, although the term "mesogenic" is not expressly spelled out in either application. My conclusion is based on the following facts:

5. All Newcastle Disease Virus strains are categorized into three types, lentogenic, mesogenic, or velogenic, according to their effect on chickens embryos, as measured by the mean death time of the minimum lethal dose. See, e.g., Hanson and Brandly, *Science*, 122, 156-157, 22 July 1955 (attached). Velogenic strains are highly pathogenic to chickens and require special facilities for their handling. Less virulent are mesogenic and lentogenic strains which form the basis for chicken vaccines. Any skilled

worker in the art would be knowledgeable about the three categories of NDV virus, including specific facts about their properties and characteristics.

6. Throughout the specification, Newcastle Disease Virus is generally described as useful to treat and detect cancers. See, e.g., '519, Page 3, lines 10-20. Because there are only three general categories, the skilled worker reading either disclosure would have necessarily and inevitably recognized that the invention could be practiced with each of three categories of virus. Thus, although the specification does not literally state that a lentogenic, mesogenic, or velogenic strain could be administered to treat or detect cancer, the skilled worker would have envisaged such words as if expressly written since they are literally embodied by the term Newcastle Disease Virus, i.e., together they are synonymous with the NDV genus.

7. As for "mesogenic" in particular, it even more clearly would be recognized necessarily by a skilled worker. The specification expressly discloses that NDV strain M, Mass-MK107, is effective to treat cancer. '519, e.g., Page 18. MK107 is well known as a mesogenic strain and would be readily recognized as such by the skilled worker. See, e.g., Hanson and Brandly, *Science*, 122, 156-157, 1955, especially Table 1. The disclosure of a mesogenic strain, i.e., MK107, coupled with the generic disclosure of Newcastle Disease Virus which comprises lentogenic, mesogenic, and velogenic strains, clearly describes to a skilled worker in the art, the concept of administering mesogenic Newcastle Disease Virus to treat or detect cancer.

I hereby declare that all statements made herein of my own knowledge are true, rue and that all statements made on information and belief are believed to be and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: 3/18/96 Leonard J. Heldman Jr.

Conrad J. Heilman Jr., Ph.D.
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SUMMARY

Ph.D. scientist with executive management experience in biotechnology and the pharmaceutical industry. Scientific expertise in viral vaccine research, viral diagnostics, pharmaceuticals, gene and cellular therapy. Managerial experience in molecular virology, applied molecular biology and gene therapy.

EXPERIENCE

Pro-Virus, Inc., Rockville, MD **1994-Present**

Vice President of Research

Established a new gene therapy company from its inception to a functional company with involvement in licensing, legal agreements, strategic planning, research, project development, recruiting, and FDA interactions.

- Established a Cooperative Research and Development Agreement (CRADA) with the National Institute of Neurologic Disease and Stroke (NINDS), at the NIH, and act as principle investigator for this project at Pro-Virus.
- Direct all Pro-Virus research and head strategic planning effort for project development associated with viral and cell based therapies.
- Actively participate in research review and planning associated with our "sister" companies with which we share space and administrative services.
- Conduct technical presentations and business discussions with prospective investors and corporate partners.
- Facilitate program development through focused project management and early dialog with the FDA.

Dupont-Merck Pharmaceutical Company, Molecular Biology Department, Wilmington, DE **1990-1994**

Director, Applied Biotechnology 1/94-10/94

- Managed a group of 24 individuals, including 5 Ph.D. scientists and 19 support personnel. Coordinated and prioritized all requests from therapeutic organizations.
- Directed all research and project planning efforts.
- Scientific director for gene therapy research
- Disciplines that I managed included gene therapy, cloning and expression, fermentation (E. coli and yeast), recombinant baculovirus expression in insect cells, mammalian cell expression, protein purification, and protein biochemistry.
- Chairman of the Gene Therapy Working Group, Chairman of Animal Care and Use Committee, member of Scientific Advisory Council, member of Glenolden Central Staff, and member of Executive Director's Staff.

Research Manager, Gene Delivery 2/92-1/94

- Directed science and administered program and personnel (2 Ph.D. scientists and 4 support personnel).

- Developed novel vectors and tissue specific gene delivery systems for in vivo therapeutic use.
- Established and chaired a gene therapy working group with representation from all major research and development departments.

Research Manager, Molecular Virology 9/89-2/92

- Directed virology research and managed personnel in a group consisting of 6 Ph.D. scientists and 9 support staff. Research efforts were focused on human herpesvirus pharmaceutical targets.
- During this time I maintained a research laboratory and developed a novel, high through-put screen for antiviral therapeutics.
- Research focus on mechanisms of viral attachment and penetration.

The Dupont Co., Medical Products Department, Diagnostics Division, Virology R&D, Wilmington, DE **1988-1990**

Senior Research Virologist 2/88-9/89

- Developed next generation diagnostic assays for human retrovirus, with emphasis on HIV and HTLV viruses.
- ELISA systems in 96 well plate formats were developed using synthetic peptides, recombinant polypeptides, and virus derived proteins.
- Responsibilities included contract negotiations with outside companies, patent evaluation and monitoring of company sponsored research on HCV.

American Cyanamid Corporation, Lederle Laboratories, Department of Virus Vaccine R&D, Pearl River, NY. **1982-1988**

Senior Research Microbiologist, Herpes Simplex Virus Vaccine Project

- Established herpesvirus laboratory.
- Principle investigator leading effort to purify, characterize and test candidate HSV subunit vaccines *in vitro* and *in vivo*.
- Tested antigens derived from eukaryotic and prokaryotic systems.
- Identified lead candidate for vaccine development, scaled up production and purification for clinical development.
- Initiated research investigations into human cytomegalovirus vaccine research.

Litton Bionetics, NCI-Frederick Cancer Research Facility, Frederick, MD. **1976-1982**

Scientist I, NIH Intramural Research Support Program

- Academic research on the biochemical, immunological and structural properties of HSV-1 and HSV-2 structural polypeptides.
- Developed immunologic method to differentiate human immune response to HSV-1 and HSV-2.
- Extensive experience with protein biochemical and immunologic technologies.

PATENTS

Two issued patents, one patent application, and seven invention disclosures.

PUBLICATIONS

1. Premkumar-Reddy, E., Paul J. Price, Conrad J. Heilman and Padman S. Sarma. 1978. Spontaneous expression of endogenous type-C RNA virus by BALB/c splenic B-lymphocytes in continuous culture. *Virology* 84: 341.

2. Heilman, Jr., C. J., M. Zweig, J. R. Stephenson and B. Hampar. 1979. Isolation of a nucleocapsid polypeptide of herpes simplex virus types 1 and 2 possessing immunologically type-specific and cross-reactive determinants. *J. Virol.* 29: 34.

3. Zweig, M., J. J. Heilman, Jr., and B. Hampar. 1979. Identification of disulfide-linked protein complexes in the nucleocapsids of herpes simplex virus type 2. *Virology* 94: 442.

4. Zweig, M., C. J. Heilman, Jr., H. Rabin, R. F. Hopkins III, R. H. Neubauer and B. Hampar. 1979. Production of monoclonal antibodies against nucleocapsid proteins of herpes simplex virus types 1 and 2. *J. Virol.* 32: 676.

5. Zweig, M., C. J. Heilman, Jr., H. Rabin and B. Hampar. 1980. Shared antigenic determinants between two distinct classes of proteins infected with herpes simplex virus. *J. Virol.* 35: 644.

6. Heilman, Jr., C. J., M. Zweig and B. Hampar. 1981. Herpes simplex virus types 1 and 2 intracellular p40: Type-specific and cross-reactive antigenic determinants on peptides generated by partial proteolysis. *J. Virol.* 40: 508.

7. Zweig, M., S. D. Showalter, S. V. Bladen, C. J. Heilman, Jr. and B. Hampar. 1983. Herpes Simplex Virus type 2 glycoprotein gF and type 1 glycoprotein gC have related antigenic determinants. *J. Virol.* 47: 185.

8. Zweig, M., C. J. Heilman, Jr., S. V. Bladen, S. D. Showalter and B. Hampar. 1983. Detection in antisera of antibodies that cross-react with herpes simplex virus type 1 glycoprotein gC. *Infec. and Immun.* 41: 482.

9. Eisenberg, R. J., C. P. Cerini, C. Heilman, D. Long, M. Ponce de Leon, B. Dietzschold, E. Golub and G. H. Cohen. 1985. Synthetic glycoprotein D related peptides protect mice against herpes simplex virus challenge. *J. Virol.* 56: 1014.

10. Torseth, J. N., G. H. Cohen, R. J. Eisenberg, P. W. Berman, L. H. Lasky, C. P. Cerini, C. J. Heilman, Jr., S. Kerwar, T. C. Merigan. 1987. Native and recombinant herpes simplex virus type 1 envelope proteins induce human immune T-lymphocyte responses. *J. Virol.* 61: 1532.

11. Isola, V. J., R. J. Wisenberg, G. R. Siebert, C. J. Heilman, W. C. Wilcox, and G. S. Cohen. 1989. Fine Mapping of Antigenic Site II of Herpes Simplex Virus Glycoprotein D. J. Virol. 63: 2325-2334.

12. Kaplan, M. H., W. H. Hall, M. Susin, S. Pahwa, S. Z. Salahuddin, C. Heilman, J. Fetten, M. Coronesi, B. F. Farber, S. Smith. 1991. Syndrome of Severe Skin Disease, Eosinophilia, and Dermatopathic Lymphadenopathy in Patients with HTLV-II Complicating Human Immunodeficiency Virus Infection. Am. J. Med. 91: 300-309.

ABSTRACTS OF ORAL AND POSTER PRESENTATIONS AT NATIONAL AND INTERNATIONAL MEETINGS

1. Heilman, Jr., C. J., M. Zweig and B. Hampar. Immunoprecipitation of antigenically type-specific and cross-reactive peptides from digests of HSV-1 and HSV-2 protein p40. 5th Cold Spring Harbor Meeting on Herpesviruses, Cold Spring Harbor, NY, August 1980.

2. Heilman, Jr., C. J., C. P. Cerini, M. J. Jacoby, A. Cawein, D. W. McCoy and R. J. White. Immunologic characterization of an *E. coli* recombinant herpes simplex virus glycoprotein D related protein. 10th International Herpesvirus Workshop, Ann Arbor, MI, August 1985.

3. Heilman, Jr., C. J., S. J. Mento, A. D. Joseph, A. Cawein, C. J. Simmons, H. J. Fingar and C. P. Cerini. Milligram quantities of HSV gD-1 from infected VERO cells; purification, characterization and vaccine implications. 11th International Herpesvirus Workshop, The University of Leeds, Leeds, UK, July 1986.

4. Heilman, Jr., C. J., D. Cervelli, N. Ramachandran, and W. P. Sisk. Detection of Human HTLV-I and HTLV-II antibodies using an HTLV-I recombinant envelope antigen. 9th Annual Meeting of the ASM, Salt Lake City, UT, July 1990.

5. Heilman, Jr., C. J. and D. R. Cervelli. Epitope scanning to identify HTLV-I p19 amino acid sequences immunogenic during natural infection. VIII International Congress of Virology meeting, Berlin, FRG, August 1990.

6. Heilman, Jr., C. J. W. F. Herblin, J. L. Gross, and G. W. Book. Herpes simplex virus infectivity in FGF receptor negative and positive cell lines. XVI International Herpesvirus Workshop, Asilomar Conference Center, Pacific Grove, California, July 1991.

EDUCATION

BS, Biology, Long Island University, 1973
MS, Immunology, University of Pennsylvania, 1974
Ph.D., Virology, School of Public Health and Hygiene, The Johns Hopkins University, 1982

References will be supplied upon request.